Supplementary Material

Table S1: Trial information: the SUSTAIN 1-6 and Japanese trials

Trial	N	Randomisation	Duration Weeks	Background	Comparator
SUSTAIN 1	388	2:2:1:1	30	Drug-naïve	Placebo
SUSTAIN 2	1231	2:2:1:1	56	MET ± TZD	Sitagliptin 100 mg
SUSTAIN 3	813	1:1	56	1-2 OADs	Exenatide ER 2.0 mg
SUSTAIN 4	1089	1:1:1	30	MET ± SU	IGlar (titrated to target)
SUSTAIN 5	397	2:2:1:1	30	Basal insulin ± MET	Placebo
SUSTAIN 6	3297	1:1:1:1	104	Drug-naïve/1-2 OADs/Basal or premix insulin ±1-2 OADs	Placebo + SOC
SUSTAIN JP Mono	308	1:1:1	30	Drug-naive	Sitagliptin 100 mg
SUSTAIN JP OAD	601	2:2:1	56	Treatment naïve/ 1 OAD	1 OAD (DPP-4i; biguanide; SU; glinide, α-GI or TZD)

α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; IGlar, insulin glargine; JP, Japanese; MET, metformin; Mono, monotherapy; OAD, oral antidiabetic drug; SOC, standard of care; SU, sulphonylurea; TZD, thiazolidinedione.

Table S2: Assessment of diabetic retinopathy across the phase 3a SUSTAIN clinical trial programme

	Phase 3a pool	SUSTAIN 6 (CVOT)
At baseline		
Medical history	X	X
Dedicated DR history form		X
During the trials		
AE reporting	X	X
Adjudication of DR complications		X
Fundoscopy/Fundus photography		
Baseline	X	X
EOT and at premature treatment discontinuation	JP SUSTAIN trials only	X
At year 1 and year 2		X

The phase 3a pool includes SUSTAIN 1–5 and the Japanese trials, but not SUSTAIN 6. AE, adverse event; CVOT, cardiovascular outcomes trial; DR, diabetic retinopathy; EOT, end of treatment; JP, Japanese.

Table S3: Baseline characteristics of all patients and patients with EAC-confirmed events of diabetic retinopathy complications in SUSTAIN 6

	Patients with EAC-confirmed events of DR complications in-trial		Overall trial population	
	Semaglutide (N=50)	**Placebo (N=29)**	**Semaglutide (N=1648)**	**Placebo (N=1649)**
Age (years), Mean (SD)	63.0 (5.6)	61.8 (7.0)	64.7 (7.2)	64.6 (7.5)
Sex				
Male, N (%)	34 (68.0)	17 (58.6)	1013 (61.5)	989 (60.0)
Female, N (%)	16 (32.0)	12 (41.4)	635 (38.5)	660 (40.0)
Diabetes duration (years), Mean (SD)	17.08 (9.15)	18.29 (6.89)	14.17 (8.20)	13.60 (8.02)
HbA_{1c} (%), Mean (SD)	9.18 (1.95)	9.71 (1.83)	8.70 (1.45)	8.70 (1.47)
Insulin treatment, N (%)	38 (76.0)	22 (75.9)	956 (58.0)	957 (58.0)
Basal insulins, N (%)	14 (28.0)	12 (41.4)	515 (31.3)	426 (25.8)
Premix insulins, N (%)	24 (48.0)	10 (34.5)	441 (26.8)	692 (42.0)
History of DR, N (%)				
Yes	42 (84.0)	24 (82.8)	510 (30.9)	459 (27.8)
Proliferative	14 (28.0)	9 (31.0)	103 (6.3)	99 (6.0)
Macular oedema	3 (6.0)	1 (3.4)	16 (1.0)	15 (0.9)
Laser therapy/ intravitreal agents	10 (20.0)	4 (13.8)	59 (3.6)	53 (3.2)
Surgery	2 (4.0)	2 (6.9)	14 (0.8)	10 (0.6)
Non-proliferative	26 (52.0)	13 (44.8)	402 (24.4)	348 (21.1)
Macular oedema	7 (14.0)	4 (13.8)	31 (1.9)	33 (2.0)
Laser therapy/ intravitreal agents	10 (20.0)	5 (17.2)	57 (3.5)	43 (2.6)
Surgery	0 (0.0)	0 (0.0)	5 (0.3)	5 (0.3)
Unknown type	2 (4.0)	2 (6.9)	5 (0.3)	12 (0.7)
Macular oedema	0 (0.0)	0 (0.0)	0	1 (0.1)
Laser therapy/intravitreal agents	1 (2.0)	0 (0.0)	2 (0.1)	2 (0.1)
No	5 (10.0)	4 (13.8)	1023 (62.1)	1089 (66.0)
Unknown	3 (6.0)	1 (3.4)	115 (7.0)	101 (6.1)
SBP (mmHg), Mean (SD)	144.5 (25.02)	130.8 (17.15)	136.0 (17.47)	135.3 (16.82)

EAC, (external) event adjudication committee; DR, diabetic retinopathy; SBP, systolic blood pressure; SD, standard deviation.

Table S4: Patients with diabetic retinopathy complications in SUSTAIN 6

	Semaglutide		Placebo		Total	
	N (%)	E	N (%)	E	N (%)	E
Diabetic retinopathy complications	50 (3.0)	62	29 (1.8)	36	79 (2.4)	98
Need for retinal photocoagulation	38 (2.3)	43	20 (1.2)	24	58 (1.8)	67
Need for treatment with intravitreal agents	16 (1.0)	18	13 (0.8)	14	29 (0.9)	32
Vitreous haemorrhage	16 (1.0)	19	7 (0.4)	8	23 (0.7)	27
Onset of diabetes-related blindness*	5 (0.3)	5	1 (0.1)	1	6 (0.2)	6

*Defined as Snellen visual acuity of 20/200 (6/60) or less, or visual field of less than 20 degrees, in the better eye with best correction possible.
CI, confidence interval; E, events.

Table S5: Clinical details of the EAC-confirmed diabetes-related blindness cases in SUSTAIN 6

	Semaglutide					Placebo
	1	2	3	4	5	6
Age (years)	57	70	62	67	71	52
Country	Australia	UK	US	US	US	US
Eye-related medical history prior to event	• PDR • Macular oedema • Macular ischaemia • Laser tx or IV agents • Cataract	• PDR • Recurrent VH • Laser tx or IV agents • Cataract	• PDR • Retinal haemorrhage • Laser tx or IV agents • Cataract	• PDR • Recurrent VH • Laser tx or IV agents • Cataract surgery	• PDR • Laser tx or IV agents • Cataract surgery • Glaucoma	• No known diabetic retinopathy
Diabetes duration (years)	13.5	13.2	20.5	20.5	43.3	25.2
HbA_{1c} at randomisation (%)	8.8	8.7	8.9	8.9	7.5	9.7
ΔHbA_{1c}, (%) at Week 16	-2.3	-1.0 at Week 8	-2.7	-1.6	-0.5	-0.5
Insulin therapy prior to event (Y/N)	Y	Y	Y	Y	Y	Y
Onset of event (day number)	15	60	121	304	323	239
Latest vision available	Not blind 18 months after event	Not blind 2 years after event	Not blind 21 days after event	Unavailable	Unavailable Subject died	Blind 16 days after event

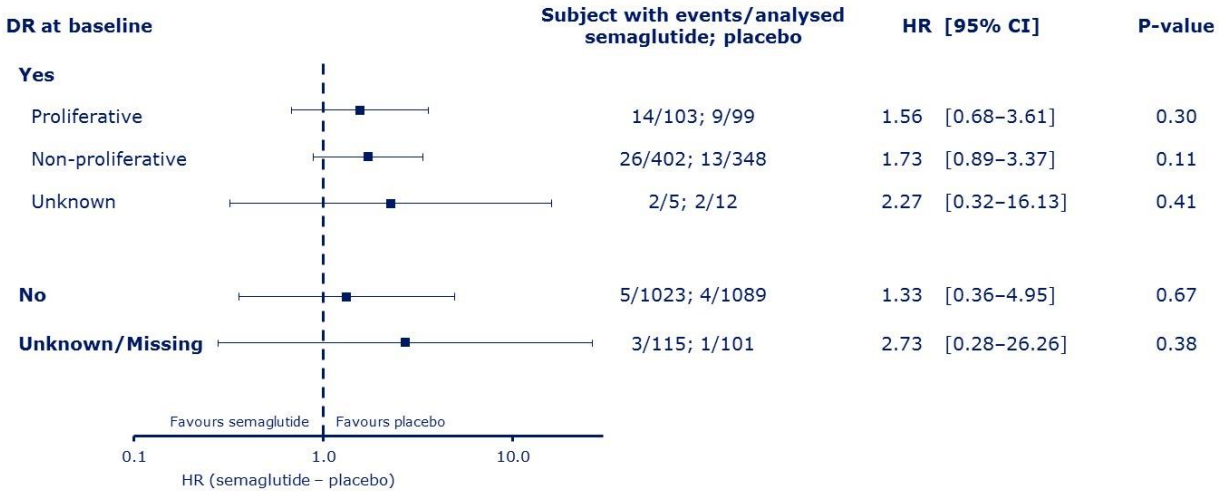
ΔHbA_{1c}, change in HbA_{1c}; IV, intravitreal; N, no; PDR, proliferative diabetic retinopathy; Pt patient; tx, treatment; VH, vitreous haemorrhage; Y, yes. Diabetes-related blindness is classified as onset of diabetes-related blindness, defined as Snellen visual acuity of 20/200 [6/60] or less, or a visual field of 20 degrees or less, in the better eye with the best correction possible.

Table S6: Fundoscopy/fundus photograph results from SUSTAIN 6

	SUSTAIN 6	
	Semaglutide Left,%/Right,%	Placebo Left,%/Right,%
Baseline	100/100	100/100
Normal	50/50	54/53
Abnormal, not clinically significant	37/38	36/36
Abnormal, clinically significant	10/10	9/10
Missing	2/2	1/1
Normal at baseline	100/100	100/100
Normal at EOT	75/75	72/72
Abnormal, not clinically significant at EOT	11/11	13/13
Abnormal, clinically significant at EOT	2/2	2/3
Missing	12/12	12/13
Abnormal, not clinically significant at baseline	100/100	100/100
Normal at EOT	15/16	18/18
Abnormal, not clinically significant at EOT	70/70	68/68
Abnormal, clinically significant at EOT	3/2	2/3
Missing	12/12	12/11
Abnormal, clinically significant at baseline	100/100	100/100
Normal at EOT	13/13	20/22
Abnormal, not clinically significant at EOT	42/40	28/26
Abnormal, clinically significant at EOT	32/33	41/39
Missing	13/14	12/13

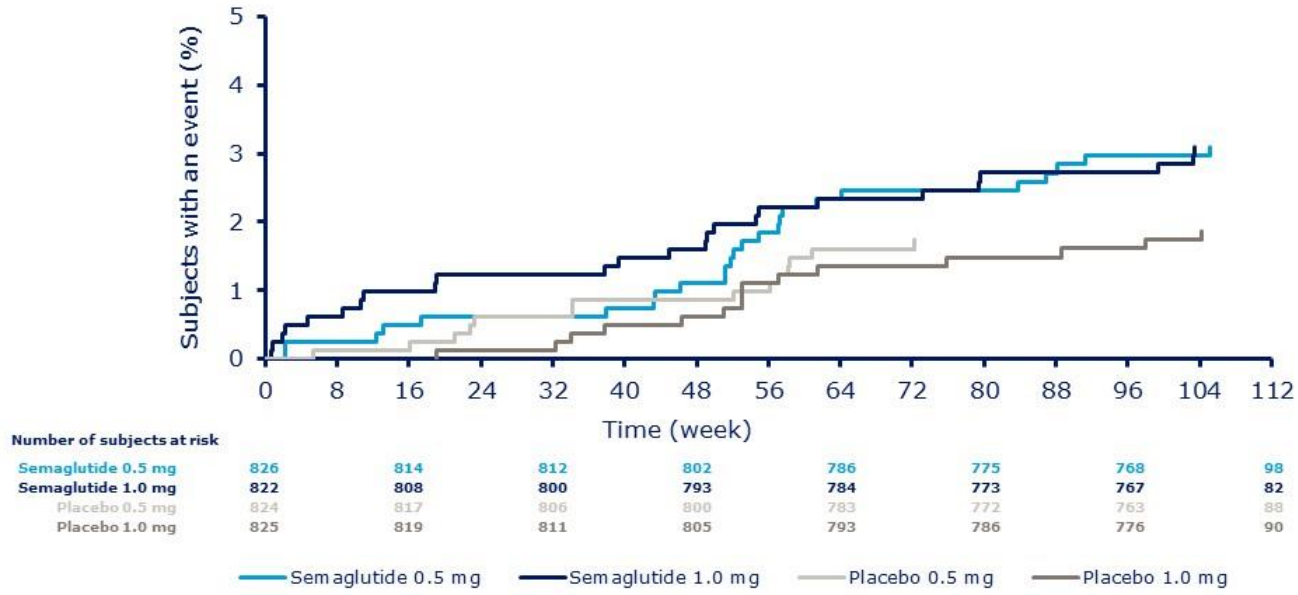
EAC, (external) event adjudication committee.

Figure S1: Time to first EAC-confirmed diabetic retinopathy complication in SUSTAIN 6 by baseline diabetic retinopathy type



CI, confidence interval; DR, diabetic retinopathy; HR, hazard ratio. Estimates are from an unstratified Cox proportional hazards model with the interaction between treatment (semaglutide, placebo) and baseline DR type (5 levels) as fixed factor.

Figure S2: Kaplan–Meier plot showing time to first EAC-confirmed diabetic retinopathy complication in SUSTAIN 6 for individual dose arms



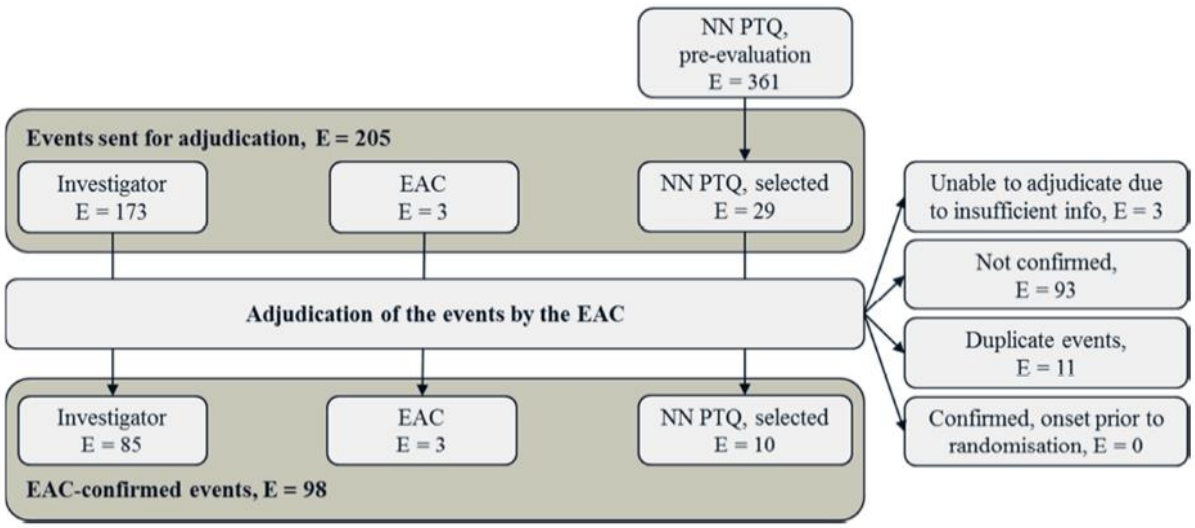
EAC, (external) event adjudication committee; EOT, end of treatment.

Supporting Information, File S1

For the adjudication of DR complications, the investigator was required to provide the following source documents to the EAC: detailed event electronic case report form (eCRF); admission history and physical examination, detailed ophthalmology consultation notes (including the times of symptom onset and resolution and physical examination findings); imaging study reports (e.g. fundus photograph, optical coherence tomography, retinal digital images, ultrasound images or fluorescein angiograms); surgical reports; and discharge summaries (if applicable). Adjudicators could also identify additional events while reviewing source documents.

The majority of events were captured via investigator reporting. The sponsor (Novo Nordisk A/S) conducted additional searches of the trial database to identify any potentially missed events.

A total of 98 events of DR complications were confirmed by the EAC. A summary of the how the events were identified is included below:



EAC, (external) event adjudication committee; NN, Novo Nordisk; PTQ, preferred term query.

Supporting Information, File S2

Post hoc subgroup analyses, conducted for time to first EAC-confirmed DR complication using an unstratified Cox proportional hazards model, with an interaction between treatment (semaglutide, placebo) and subgroup variable as fixed factor, considered the following variables: gender, baseline age, duration of diabetes, HbA_{1c} level and baseline insulin, diabetic retinopathy status (Yes, No, Unknown/missing), diabetic retinopathy type (Yes – proliferative, Yes – non-proliferative, Yes – unknown type, No, Unknown/missing), fundoscopy, macular oedema and hypertension, and geographic area.

A similar *post hoc* mediation analysis to that with change in HbA_{1c} (percentage-points) at Week 16 was conducted with change in systolic blood pressure (SBP) (mmHg) at Week 16 as the covariate. Confounding baseline variables were: SBP, DR, and duration of diabetes. Additional time points were also investigated.

For the unstratified Cox proportional hazards model exploring the impact of insulin use on the risk of DRC, insulin use was defined on a subject level as a binary time-dependent variable (Yes/No): at baseline, if the subject was randomised on insulin, 'Yes', if not, 'No'. For 'No' patients at baseline, this variable was changed to 'Yes' at the time of initiation of insulin during trial if this occurred prior to a DRC event or censoring. Two HRs were estimated from this model: one for the effect of semaglutide in patients with insulin use; one for the effect of semaglutide in those with no insulin use during the trial. This analysis was done for the entire population and by baseline retinopathy (Yes, No, Unknown/missing).

A *post hoc* mediation analysis was conducted using an unstratified Cox proportional hazards model which, in addition to treatment (semaglutide, placebo) as a fixed factor, included average SBP as a time-varying covariate as well as the confounding variables: 'SBP at baseline', 'DR at baseline' (Yes/No/Unknown) and 'baseline duration of diabetes'.

Missing values of SBP were imputed as predicted values from a mixed model for repeated measurements. The average SBP was calculated at each scheduled assessment time as an updated, time-weighted mean.

Supporting Information, File S3

The HR for the expanded mediation analysis assessing the effect of change in HbA_{1c} at Week 16 with other baseline variables, including hypertension as measured by baseline SBP, triglycerides, LDL-cholesterol and insulin use (Yes/No), was comparable to the HR for change in HbA_{1c} at Week 16 (HR, 1.29 [p=0.37] versus HR, 1.22 [p=0.48]) and therefore provided no additional explanation for the excess risk in DRC observed with semaglutide versus placebo; there was no imbalance in the added variables at baseline.

In SUSTAIN 6, there was a small difference in SBP at baseline between those with and without DRC (139.5 [23.30] and 135.5 [16.96] mmHg, respectively). At Week 104, there was no significant difference in mean SBP with semaglutide 0.5 mg versus placebo 0.5 mg (p=0.10). SBP was significantly lower at Week 104 with semaglutide 1.0 mg versus placebo 1.0 mg (p<0.001).

A *post hoc* mediation analysis, controlling for SBP reduction at Week 16, indicated that the reduction in SBP did not further explain the treatment effect of semaglutide versus placebo, as the HR remained similar to the HR for the DRC endpoint (HR, 1.66 [p=0.03] versus 1.76 [p=0.02], respectively).

Furthermore, a *post hoc* mediation analysis, assessing the effect of average SBP as a time-varying covariate on time to first DRC, indicated no mediation of the treatment effect by greater SBP load over time with semaglutide versus placebo, as the HR was 1.66 [p=0.03], similar to that for the DRC endpoint (HR, 1.76 [p=0.02]).